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Apgar score of dog puppies delivered by cesarean section using alfaxalone or propofol for anesthesia induction

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CONTENTS

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1. Summary

The effects of alfaxalone (A) and propofol (P) on neonatal vitality were studied in 22 bitches and puppies after their use as anesthetic induction agents for emergency cesarean section. After assessment that surgery was indicated, bitches were randomly allocated to receive either A 1 to 2 mg/kg or P 2 to 6 mg/kg BW iv for anesthetic induction given to effect to allow endotracheal intubation. Anesthesia was maintained with isoflurane in oxygen. Neonatal vitality was assessed using a modified Apgar score that took into account heart rate, respiratory effort, reflex irritability, motility, and mucous membrane color (maximum score = 10); scores were assigned at 5, 15, and 60 min post-delivery. Neither the number of puppies delivered nor the proportion of surviving puppies up to 3 months post-delivery differed between groups. Anesthetic induction drug and time of scoring were associated ($p<0.001$) with the Apgar score, but delivery time was not. Apgar score increased in both groups from 5 to 60 min post-delivery. Apgar scores in the group A were greater than those in group P at 5, 15, and 60 min post-delivery; the overall estimated score difference between the groups was 3.3 (CI 95%: 1.6 to 4.9; $p<0.001$). In conclusion, both A and P can be safely used for induction of anesthesia in bitches undergoing emergency C-section. Although puppy survival was similar after the use of these drugs, A was associated with better neonatal vitality during the first 60 min post-delivery.

Keywords: puppy; cesarean section; alfaxalone; propofol; Apgar score

2. Introduction

Approximately 16 % of all bitches suffer from dystocia and greater than 60 % of bitches with dystocia need a cesarean section (C-section). Performing an emergency C-section is a common procedure in small animal obstetrics [1,2] and various anesthetic techniques have been reported [2-5]. All anesthetic drugs, including inhalant anesthetic agents, cross the placenta and the blood-brain barrier of the fetus, leading to a variable extent of neonatal depression [3-5]. The anesthetic protocol selected should be optimized for both dam and fetus with minimal neurological and cardiorespiratory depression [4]. Maternal lethargy and reduced neonatal vitality during the critical first postoperative hours result in reduced colostrum intake and increased mortality rate of the puppies [3,5-7]. Currently, many veterinarians use propofol followed by isoflurane for induction and maintenance of anesthesia for C-section [2,6-9].

Anesthetic induction with propofol and maintenance with isoflurane improves puppy vigor and newborn survival rates compared to other general anesthetic protocols and is considered almost equal to epidural anesthesia [6-8]. Recovery from propofol anesthesia is normally rapid and smooth due to rapid redistribution and metabolism. Although propofol crosses the placental barrier, it is rapidly cleared from the neonatal circulation [5,10,11]. The neuroactive steroidal combination Saffan (a mixture of alfaxalone and alfadolone solubilized in 20% of a polyoxyethylated castor oil called Cremophor EL) was used widely in the late twentieth century in cats and was considered to be a very safe agent for anesthesia induction and short surgical procedures [12]. In dogs, its use was limited due to Cremophor EL-induced histamine release that resulted in decreased arterial blood pressure, urticaria and skin erythema, and serious anaphylactic reactions [13]. However, after pre-anesthetic medication with an antihistaminic agent, Bomzon et al. [14] reported Saffan to be a safe and predictable anesthetic agent for dogs undergoing C-section, and to be superior to thiopental. In the last decade, a new Cremophor EL-free formulation of alfaxalone has been developed for use in small animals (Alfaxan®, Vétoquinol, UK). The new formulation uses a cyclodextrin base (2-hydroxypropyl-β-cyclodextrin, HPCD) as solubilizing agent and does not cause histamine release [15,16]. Alfaxalone was been shown to provide rapid and smooth induction of anesthesia with rapid recovery of consciousness and minimal respiratory depression. It also has a wide margin of safety and short total body clearance and mean plasma terminal half-life [16,17]. Although alfaxalone is currently routinely used for induction of anesthesia in dogs

and cats in many countries, it has never been evaluated in regard to its safety for C-section.

The objectives of this study were to evaluate, in a clinical setting, the effects of alfaxalone as an anesthetic induction agent for dogs undergoing emergency C-section and to compare neonatal vitality following either alfaxalone or propofol anesthetic induction.

3. Material and methods

3.1. Animals

The local ethics committee approved the study. Twenty-two bitches presented to the Clinic for Reproductive Medicine of the University of Zurich were used in this study. The group receiving alfaxalone (n=11) consisted of three Chihuahuas, two West Highland White Terriers, and one Poodle, Dachshund, Yorkshire Terrier, Eurasian Dog, Bichon Frisè and small Mixed Breed dog. The group receiving propofol (n=11) consisted of two Chihuahuas, two French Bulldogs, and one Yorkshire Terrier, Pug, Bernese Mountain Dog, Bolonka Zwetna, Australian Cattle Dog, Golden Retriever and small Mixed Breed dog. Age of the bitches ranged from 1 to 11 years (3.0, 1.3 to 6.2 years; mean, 10-90 percentile range) and body weight (BW) ranged from 1.6 to 51 kg (7.3, 2.1 to 28.4 kg). C-section was indicated due to dystocia in all cases due to poor general condition of the dam, birth canal obstruction, fetomaternal disproportion, fetal malposition, fetal heart rate of one or more puppies less than 180 bpm over several minutes, dystocia with more than two puppies remaining to deliver, and/or unsuccessful medical management of dystocia [18].

3.2. Anesthesia

All bitches started to receive intravenous fluids immediately after presentation (Lactated Ringer's solution, 10 to 20 mL/kg BW/h); in case of poor general condition or severe dehydration, HAES-steril 10% (Fresenius Kabi, Germany) was added (1 to 2 mL/kg BW/h). Infusion was maintained until the bitch had fully recovered from anesthesia. Before induction of anesthesia, bitches were pre-oxygenated for 5 min using flow-by oxygen at 2 L/min and received a single intravenous dose of cefazolin 20 mg/kg BW (Kefzol®; Teva Pharma,

Switzerland). Sedatives and analgesics were not administered until all puppies were delivered. For anesthesia induction, bitches were randomly assigned to received either alfaxalone (Alfaxan®; Vétoquinol, UK) 1 to 2 mg/kg BW or propofol (Propofol 1% MCT; Fresenius Kabi, Germany) 2 to 6 mg/kg BW for anesthetic induction. Both drugs were administered intravenously to effect to allow endotracheal intubation. The surgeons and the observer performing post-anesthetic evaluations were blind to the induction agent used.

After intubation, anesthesia was maintained with isoflurane (Isoflo®; Abbott, Dr. E. Graeub AG, Switzerland) in oxygen at the dosage to effect. Immediately after delivery of the last puppy, a continuous rate intravenous infusion of fentanyl (Sintetica SA, Switzerland) 5 mcg/kg BW/h was started and stopped at the end of surgery. All bitches received intravenous buprenorphine (Temgesic®; Reckitt Benckiser, Switzerland) 14 mcg/kg BW and carprofen (Rimadyl®; Pfizer AG, Switzerland) 4 mg/kg BW 20 min before the end of surgery. Total duration of anesthesia was defined as time from anesthetic induction until the stop of isoflurane inhalation. Delivery time was defined as time from anesthetic induction until delivery of the last puppy.

3.3. Post-delivery neonatal care and assessment

Immediately after delivery, puppies had fluid cleared from the upper airways by suctioning and were rubbed and blow-dried on warm bedding. All puppies were oxygenated using flow-by oxygen at 2 L/min. If breathing did not start immediately, gentle mouth-to-nose breathing was performed in order to expand the lungs. If breathing was still inadequate, a centrally acting analeptic was administered (Respirot®; Novartis Tiergesundheit AG, Switzerland) at a dosage of one to two drops given orally and received a single subcutaneous bolus of warmed glucose 5 % (3 to 5 mL/100 g BW). Resuscitation was attempted for at least 30 min if a heartbeat was detected. The umbilical cord was ligated 0.5 to 1 cm from the abdominal wall and the umbilical stalks were disinfected with a weak iodine solution. Body weight was recorded and a detailed clinical examination was performed. After stabilization, puppies were transferred to a newborn incubator (see [2] for details).

A modified Apgar score for puppies developed by Veronesi et al. [9] was used to objectively assess neonatal vitality. The following parameters were evaluated: heart rate, respiratory effort (respiratory rate and type of crying), reflex irritability, motility, and mucous membrane

color. Each parameter was rated as 0 (absent), 1 (detectable, weak) or 2 (detectable, strong). The sum of all parameters, up to a maximum of 10, provided the total Apgar score. Puppies were assessed at 5, 15 and 60 min post-delivery.

3.4. Statistical Analysis

Statistical analysis was performed using Stat View 5.0® (SAS Institute Inc., Cary, NC, USA). Linear mixed models were performed with R (Team 2010) and the packages nlme [19]. All continuous variables were summarized by descriptive statistics as median values, 10-90 percentile ranges, and box plots. Mann-Whitney U-test was performed to evaluate group differences in preoperative (age, body weight, maternal body temperature, heart rate, respiratory rate, PCV) and intra- and/or post-operative parameters (body temperature, heart rate, respiratory rate, blood pressure, total duration of anesthesia, delivery time of puppies, litter size). Chi-square test was used to evaluate group differences regarding the method of surgery (proportion of bitches undergoing C-section with versus without ovariohysterectomy), parity (proportion of bitches with no versus one or more previous pregnancies), and neonatal survival (proportion of life and dead puppies). Linear mixed models, accounting for clustering within puppy and bitch, were used to evaluate the association of pre- and intra-operative factors (induction agent and delivery time of puppies) with the Apgar score. Model selection (i.e. fitting variables in the model) was based on the Akaike information criteria (AIC). Model validation was based on checking the residuals for homogeneity and independence. Results are presented as the estimated difference between the two groups and their corresponding 95% confidence interval (95 % CI).

4. Results

Pre- and intra-operative parameters did not differ between the groups (Table 1). Total litter size ranged from 1 to 10 puppies (4.5, 2.0 to 7.6 puppies) and a median of 3.0 (1.0 to 7.0) puppies were delivered by C-section; no differences were observed between the groups (Table 1). Birth weights ranged from 71 to 524 g and were considered to be within the normal range for each breed. Five bitches of alfaxalone group and six bitches of propofol group were ovariohysterectomized as per owner's request after the C-section. Maternal recovery was

uneventful and rapid in both groups.

Neither the number of puppies delivered nor the proportion of surviving puppies at 60 min, 24 hours, 3 days, 3 weeks, or 3 months post-delivery differed between groups (Table 2). Anesthetic induction drug and time of scoring were associated ($p<0.001$) with the Apgar score, but delivery time was not. Apgar score increased in both groups from 5 to 60 min post-delivery. At the first assessment 5 min after birth, the proportion of puppies in alfaxalone group (n=41) with high (7 to 10), medium (4 to 6), and low (0 to 3) Apgar scores were 68, 15, and 17%, respectively. These proportions for puppies in the propofol group (n=32) were 19, 31, and 50%, respectively. Apgar scores in the alfaxalone group were greater than those in propofol group at 5, 15, and 60 min post-delivery; the overall estimated score difference between the groups was 3.3 (CI 95%: 1.6 to 4.9; ($p<0.001$); Figure 1).

5. Discussion

The present study demonstrates that alfaxalone is suitable for anesthesia induction in bitches undergoing C-section. Alfaxalone induction resulted in significantly improved neonatal Apgar scores compared to propofol. With alfaxalone induction, newborn puppies recovered from anesthesia more quickly, which might facilitate colostrum uptake in the first hours post-delivery.

Use of the Apgar scoring system adapted for puppies by Veronesi et al. [9] at 5, at 15 and at 60 min post-delivery allowed for objective comparison between anesthetic drugs. Several recent studies have examined the association between Apgar score and short-term survival prognosis, umbilical vein lactate measurement, blood gas assessment and acid base changes in neonatal dogs [9,20-22]. Groppetti et al. found that Apgar scores and umbilical lactate concentration at birth, an important marker of fetal and neonatal distress, were significantly correlated in puppies [22]. The value of the Apgar score in predicting short-term survival is less clear. Even though one study reported a significant correlation between moderate to low Apgar scores and the percentage of mortality shortly after birth, findings from another group did not support this [9,22]. However, it is clearly shown that C-section has an impact on Apgar scores. Using propofol induction, Groppetti et al. observed low viability and poor

Apgar scores in 100% and 92% of puppies born from emergency and elective C-sections, respectively, compared to only 30% of pups with low Apgar scores delivered vaginally [22]. In contrast to that study, we found much better neonatal vitality after emergency C-section not only with alfaxalone but also after propofol induction, as only 17% and 50% of puppies were considered to have poor Apgar scores at 5 min after delivery, respectively. In agreement with previous studies, Apgar scores in our study improved considerably in the first 60 min post-delivery [20,21].

The most critical moments in a puppy's life are the time interval between delivery and first breath, time of first contact with and acceptance by the dam. Both the neonate's ability to breathe and the dam's ability to take care of her offspring are significantly influenced by the anesthetic protocol chosen to perform a C-section [3,5,23], for which various protocols have already been reported (see reviews [2,3]). Although induction with propofol followed by isoflurane maintenance is considered to be superior to other general anesthetic protocols and equal to epidural anesthesia [3,6-8], in individual cases other protocols may be preferable according to the clinician's experience or the general status of the dam, e.g. to minimize cardiorespiratory depression in a critical patient [2,3,23].

Propofol and alfaxalone are both short-acting hypnotic agents and provide rapid induction and recovery from anesthesia. Both agents cross the placental barrier [5,24]. Alfaxalone has hypnotic, muscle relaxant, and limited antinociceptive effects due to its interaction with $GABA_A$ receptors and enhancement of GABA neurotransmission [25]. Alfaxalone induces a dose-dependent decrease in blood pressure caused by peripheral vasodilation [17]. In clinically effective dosages, alfaxalone does not impair stroke volume ratio [17,24]. Propofol also enhances GABA neurotransmission and has no analgesic effect [26]. Compared with alfaxalone, propofol is reported to cause more cardiorespiratory depression and to increase $PaCO_2$ [17,24], which may have negatively influenced puppy vitality in the current study.

Anesthetic recovery of the dams in the current study was smooth and rapid with both anesthetic agents. This is in disagreement with Jiménez et al., who described poorer recovery quality alfaxalone induction compared to propofol [27]. However, the results may have been influenced by the neurological condition of the dogs in their study. An additional advantage of alfaxalone for practitioners is its longer shelf life and its higher resistance against microbial growth compared to propofol [28].

In conclusion, both alfaxalone and propofol can be safely used for induction of anesthesia in bitches undergoing emergency C-section. Although puppy survival up to 3 months after birth was similar after the use of these drugs, alfaxalone was associated with better neonatal vitality during the first 60 min post-delivery.

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7. Tables

Table 1

Median (10-90 percentile range) pre- and intra-operative parameters in bitches undergoing C-section using alfaxalone or propofol for anesthesia induction (n=11/group).

	Alfaxalone	**Propofol**
Pre-operative		
Age (y)	3.0 (1.3-7.9)	3.3 (1.6-6.3)
Parity	1 (1-2)	1 (1-2)
Body weight (kg)	7 (2-16)	8 (2-44)
Temperature (°C)	37.8 (37.0-38.8)	37.9 (36.9-38.4)
Heart rate (bpm)	140 (120-180)	120 (84-160)
Respiratory rate* (cpm)	150 (33-150)	150 (46-150)
Packed cell volume (%)	39 (32-42)	38 (27-46)
Total protein (g/L)	60 (52-70)	59 (52-700)
Intra-operative		
Anesthesia duration (min)	98 (54-117)	90 (67-126)
Temperature (°C)	36.5 (35.5-37.3)	36.5 (33.6-37.6)
Heart rate (bpm)	126 (104-139)	121 (99-148)
Mean blood pressure (mmHg)	66 (28-72)	68 (46-107)
Delivery time (min)	23 (10-38)	25 (17-42)
Puppies delivered by C-section	4.0 (1.6-6.4)	2.0 (1.0-8.2)

*When the bitch was panting, a cpm of 150 was uniformely given as respiratory rate.

Table 2

Puppy survival according to time post-delivery after using alfaxalone or propofol for anesthesia induction for C-section (n=11 bitches/group).

	Alfaxalone	**Propofol**
Total puppies[1]	36	45
Live at birth (%)	32 (89)	41 (91)
Live after 60 minutes (%)[2]	30 (83)	41 (91)
Live after 24 hours (%)	30 (83)	41 (91)
Live after 72 hours (%)	30 (83)	41 (91)
Live after 3 weeks (%)3	30 (83)	39 (87)
Live after 3 months (%)	30 (83)	39 (87)

[1]Eight puppies born dead were from six different litters. One litter from each anesthetic group had two of those puppies, and the remaining four litters (two per group) had one in each born dead. Six of them had no visible malformations and two puppies from one litter were mummified.

[2]The two puppies that died within the first 60 minutes after delivery in the alfaxalone group had an Apgar score of zero at delivery.

[3]One puppy died three days and another puppy from a different litter died five days after delivery in the propofol group. The cause of death was not determined, but other littermates remained healthy until 3 months of age.

8. Figure

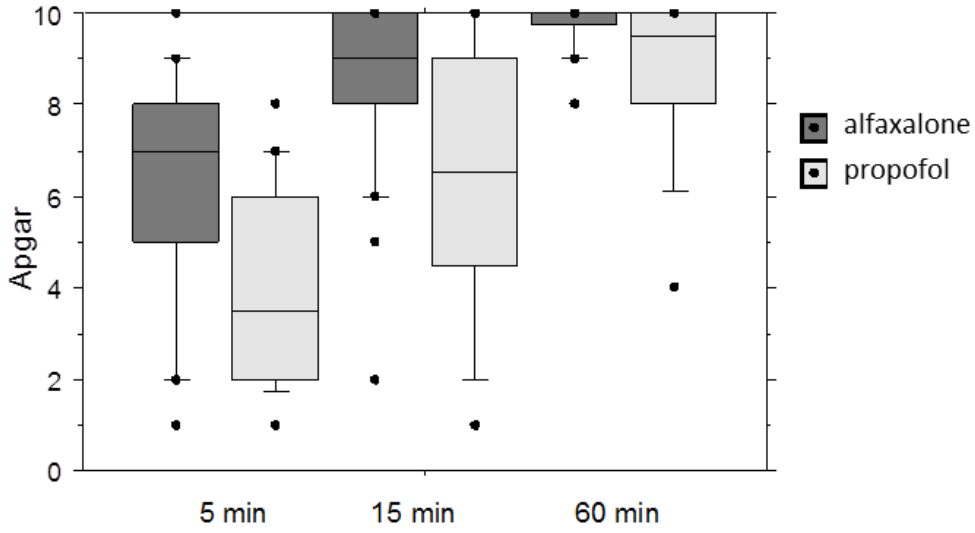

Fig 1.: Box and whisker plot of Apgar scores of puppies whose dams undergone C-section using alfaxalone (n=11 bitches and 32 puppies) or propofol (n=11 bitches and 41 puppies) for anesthesia induction at 5, 15 and 60 min post-delivery. Apgar scores measured over time differed ($p<0.001$) between groups.

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